Side Effects of Targeted Therapies: Rash

Beth Eaby-Sandy and Kathy Lynch

Objectives: *To present a thorough literature review on the assessment, grading, and treatment of rash associated with targeted therapies for cancer treatment. To identify ways that nursing can impact a patient's treatment experience by understanding and properly managing treatment for the rash.*

Data Sources: *Peer-reviewed journal articles, textbooks.*

Conclusion: *Identification and management of rash induced by targeted therapies may improve quality of life and allow patients to continue drug therapy for their cancer to offer best outcomes.*

Implications for Nursing Practice: *Nurses are in a unique position to assess, grade, and manage rash in patients receiving targeted therapies. Nurses will often be the first point of contact for the patient experiencing a rash, and the proper triage and advice on management can help the patient tolerate these drugs and enable them to remain on treatment.*

Key Words: *Papulopustular rash, EGFR rash, dermatologic toxicities*

TARGETED therapies, now a mainstay of cancer treatment, often cause a myriad of dermatologic toxicities not commonly seen with standard chemotherapy. Epidermal growth factor receptor inhibitors (EGFRIs) as a class often causes a rash, as do a number of other targeted therapies. The rash can cause a negative effect on quality of life, as well as a significant economic burden to the patient.[1,2] With timely identification and management of the rash, these targeted therapies can often be continued at a maximum tolerated dose.

Beth Eaby-Sandy, MSN, CRNP, OCN®: *Nurse Practitioner in Thoracic Oncology at the Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.* Kathy Lynch, RN, BSN, OCN®: *Director of Nursing, Regional Cancer Care Associates, Carol Simon Cancer Center, Morristown, NJ.*

Address correspondence to Beth Eaby-Sandy, MSN, CRNP, OCN®, 3400 Civic Center Blvd., 2nd floor West Pavilion PCAM, Philadelphia, PA 19104. e-mail: eabyb@uphs.upenn.edu

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Description of EGFR Rash

Epidermal growth factor (EGF) is over expressed in several tumor types, most commonly head and neck, colorectal, and lung cancers. Other cells in the body also rely on the EGF signaling pathway, particularly the epidermis. The rapidly dividing keratinocytes located in the basal and supra basal layers of the epidermis express an elevated level of EGF. Normal skin growth is maintained by EGF by regulating proliferation, maturation, adherence, and migration of cells.[3,4] Inhibition of the EGF pathway affects keratinocytes by inducing growth arrest, apoptosis, and premature differentiation.[5]

Inhibition of EGF also results in negative effects on cell growth and cellular migration and promotes attachment, resulting in a thinning of the epidermis with fewer cells migrating toward the stratum corneum, the protective barrier that helps keep the skin hydrated. The ensuing tissue damage causes the basal cells to release chemoattractants (CXCLs, CCLs) that recruit cells of the immune system. The recruited leukocytes and neutrophils then release more effector cytokines increasing the inflammation and manifesting as a papulopustular rash.[3,5,6]

The most common dermatologic toxicity experienced by patients receiving EGFRIs is the development of a papulopustular rash,[7,8] which is characterized as a sensory disturbance with erythema, eruption of pruritic and tender erythematous papules, and pustules on the face, scalp, upper chest, and back. Although the rash may appear similar to acne vulgaris, and is referred to as acneiform and acne-like, it is not typical acne and has a distinct etiology.[5,9] Unlike acne, EGFRI-associated rash does not always present with comedones (blackheads or whiteheads) and can be accompanied by pruritus. It is often responsive to anti-inflammatory agents. Most over-the-counter anti-acne agents should be avoided because of irritation and burning.[5,6] EGFR rash has been reported to have a direct effect on physical, psychosocial, and financial well-being and the patient's ability to continue on the treatment.[10,11]

Of patients treated with EGFRIs, 80% to 90% will develop a papulopustular rash of varying severity.[7,8] The rash usually peaks within the first 2 weeks and diminishes within 6 to 8 weeks. However, it can last for much longer in some cases.[9] The severity of the rash may be influenced by several factors, including therapeutic regimen, dose intensity, and certain patient characteristics. See Figures 1 and 2 for examples of typical EGFRI rash. The rash associated with monoclonal antibodies (MABs) is generally more frequent and severe. It is likely to be more pruritic and pustular and may require more aggressive intervention.[12] The pharmacokinetic properties between the agents could be responsible for this phenomenon. The tyrosine kinase inhibitors (TKIs) are taken orally on a daily basis while the MABs are infused on a weekly or biweekly schedule, accounting for potentially greater peak and trough concentrations in the MABs.[9,13] Risk factors for rash associated with the TKIs are non-smoking, fair skin, and age greater than 70.[8]

Patients with fair skin have an increased sensitivity to the damaging effects of ultraviolet (UV) sunlight and are more susceptible to developing severe EGFRI-associated skin rash than are darker skinned patients. Clinical and experimental data suggest that development of rash can be enhanced in sun-exposed areas or areas not covered by sunscreen.[6,14-17] Conversely, there are case reports that indicate rash from targeted agents is less severe in areas of the skin that have been previously radiated, likely because of loss of hair follicles and sebaceous glands.[18,19]

In a meta-analysis of over 5,000 patients, the addition of cytotoxic chemotherapy agents to cetuximab was reported to significantly increase the risk of developing a high-grade rash. It is unclear whether this increase was caused by intrinsic exacerbation by the addition of these agents or because

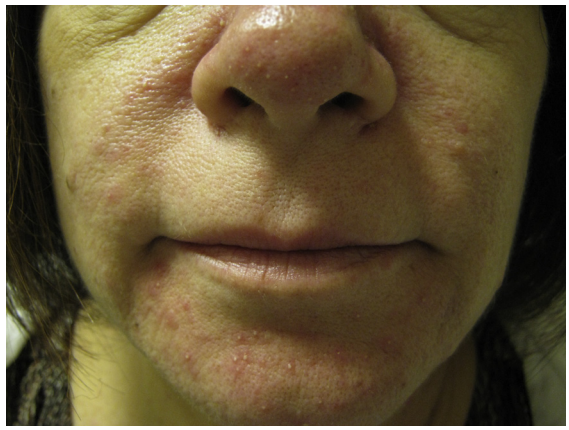

FIGURE 1. Moderate papulopustular rash from EGFRI. (Illustration appears in color on the journal's website at www.nursingoncology.com.)

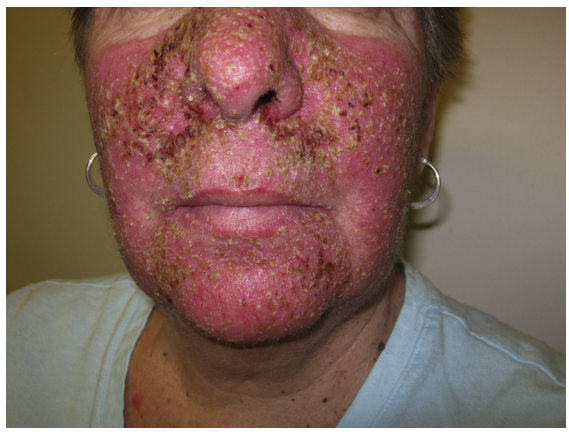

FIGURE 2. Severe or grade 3 rash from erlotinib in an EGFR mutation-positive patient 13 days after taking the drug. (Illustration appears in color on the journal's website at www.nursingoncology.com.)